Pregnancy Outcomes and Reproductive Health After Liver Transplantation

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As survival rates after liver transplantation (LT) continue to improve, long-term medical management of the LT recipient has become an important field of study. The quality of life (QOL) after LT is worse in female than in male recipients.¹ Potential factors that may impact QOL for female patients are reproductive health, pregnancy outcomes, and fertility after LT.

Since 1958, more than 14,000 female solid organ recipients worldwide have reported successful pregnancies.² Despite an expanding population of female recipients, our understanding of the implications of pregnancy for mother, child, and graft remains limited. Since the first successful pregnancy in a liver transplant patient was reported in 1978,³ a number of case series have been published, and only recently have enough data been amassed to generate credible meta-analysis and multicenter experience. Generally, outcomes of these reported pregnancies have been favorable for both mother and child. However, significant risks do exist,⁴⁻⁹ and they should be taken into consideration during preoperative and preconception counseling.

A recent meta-analysis⁴ evaluated reports from four countries of pregnancy in LT recipients that were published between 2000 and 2011. Interestingly, a higher live birth rate was found post-LT than in the general US population (76.9% versus 66.7%), and the post-LT spontaneous abortion rate was lower than that of the general US population (15.6% versus 17.1%). However, pregnancy complications were higher in the post-LT group than in the general US population, including preeclampsia (21.9% versus 3.8%), necessity for cesarean section delivery (44.6% versus 31.9%), and preterm delivery (39.4% versus 12.5%).

A large, multicenter, case-control study from the United States⁵ examined outcomes in LT patients hospitalized with

obstetric complications between 1993 and 2005. Even though most pregnancy outcomes were positive, adverse events were higher in LT recipients and their fetuses than in their age-, hospital-, and year-matched control subjects, including rates of gestational hypertension (30% versus 9%), postpartum hemorrhage (8% versus 3%), prematurity (27% versus 11%), fetal distress (10% versus 5%), growth restriction (5% versus 2%), and fetal mortality (6.3% versus 2%).

The only active database of pregnancy outcomes for female organ transplant recipients in the United States is the National Transplantation Pregnancy Registry (NTPR), which has accumulated information on 2000 pregnancies. However, the data are voluntarily provided retrospectively by transplant centers and patients, the data are not systematically collected, and the patient population largely consists of female kidney transplant recipients. The most recent publication from the NTPR cites a live birth rate between 50% and 86% for all organ transplant recipients, with a similar birth defect rate after transplantation as in the general population.⁶

A recently published, single-center outcome study from the United Kingdom⁷ affirms the potential for safe and healthy pregnancy, although acknowledging significant risk for a minority of women. With regard to graft function, 15% of pregnancies resulted in an episode of acute cellular rejection, similar to previously reported data, which occurred significantly more frequently in patients who conceived within 12 months of LT. Pregnancy was associated with graft loss in 3% of female recipients. Pregnancy outcomes after living donor LT, including rates of hypertension, fetal growth restriction, spontaneous abortion, preterm delivery, cesarean delivery, and acute rejection, appear to be similar to those reported in recipients of cadaveric LT.⁸

Abbreviations: IS, immunosuppressive; LT, liver transplantation; NTPR, National Transplantation Pregnancy Registry; QOL, quality of life.

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TABLE 1 2003 Consensus Conference of the Women's Health Committee of the American Society of Transplantation⁹

Preconception counseling	<ul style="list-style-type: none"> • Introduce during pre-LT evaluation
Timing of pregnancy	<ul style="list-style-type: none"> • Delay conception for minimum of 1 year after LT • No rejection in the past year • Stable and adequate graft function • Stable IS regimen
Management of pregnancy	<ul style="list-style-type: none"> • High-risk comanagement with transplantation specialist and maternal-fetal-medicine • IS must be maintained to avoid rejection • Prospective studies are needed to determine IS selection and dosing
Pregnancy considerations	<ul style="list-style-type: none"> • Gestational hypertension and preeclampsia • Preterm labor

In 2003, a Consensus Conference on transplant recipient reproductive health was held by the Women's Health Committee of the American Society of Transplantation in an effort to develop clinical practice guidelines for transplant specialists and obstetricians.⁹ The conference established that all pregnancies in organ transplant recipients should be considered high risk and be managed by both transplantation medicine specialists and obstetricians trained in maternal-fetal medicine in an effort to optimize maternal health before, during, and after pregnancy (Table 1).

The effects of immunosuppressive (IS) medications on pregnancy and the fetus are not well understood. Cyclosporine is known to cross the placenta and is present in breast milk.⁹ The King's College experience⁷ reported successful pregnancies in patients maintained on cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, and prednisolone, without a significant difference in reported outcomes for mother, graft, and fetus. Earlier studies have suggested a higher rate of preeclampsia, hypertension, and renal insufficiency during pregnancy in patients taking cyclosporine A.⁴ Mycophenolate is a recognized teratogen from exposure in early pregnancy. Babies born to mothers taking mycophenolate are at risk of craniofacial, auditory and cardiovascular malformations.¹⁰ Mycophenolate should be discontinued prior to conception, and women of childbearing potential who are taking mycophenolate should be counseled to avoid conception until they have stopped mycophenolate, and established stable graft function on a mycophenolate-free IS regimen. Prospectively designed studies are needed to more clearly define optimal IS regimens during pregnancy and to clarify the role of breastfeeding in the postpartum period.

The Consensus Conference recommended that, to consider pregnancy, patients should have stable allograft function without episodes of rejection in the year before conception and stable maintenance immunosuppression.⁹ It was also recommended that pregnancy be delayed for a minimum of 1 year, to minimize risks for rejection and

infection (specifically cytomegalovirus). However, this consensus is based mainly on experience with female renal transplant recipients. When considering literature specific to LT recipients, similar to renal transplant recipients, female LT recipients were considered by the Consensus Conference to be at high risk for pregnancy complications, specifically gestational hypertension, preeclampsia, and preterm labor.

Strategies for identifying women at risk for pregnancy complications after LT have not yet been developed, which presents a challenge for both preoperative and preconception counseling. Evidence suggests that counseling is limited by the lack of high-quality evidence. In a recent single-center survey, approximately one-third of female solid organ transplant recipients reported being actively counseled against pregnancy, despite the center's largely favorable pregnancy outcomes.¹¹

A separate challenge lies in preoperative counseling regarding changes in fertility potential after LT. Chronic liver failure often results in amenorrhea and resultant infertility for many women of childbearing age, likely because of a combination of hypothalamic-pituitary-gonadal dysfunction and alteration of estrogen metabolism. In two studies of menstrual function in women post-LT,^{11,12} 30% to 48% of women with chronic liver disease reported amenorrhea of greater than 1 year's duration before LT. Menstruation resumed within 1 year of LT in 95% to 100% of premenopausal women with secondary amenorrhea. If patients are not counseled appropriately before surgery, unplanned pregnancies may occur, and self-reported evidence suggests that termination of pregnancies after LT carries significant risk for the mother.¹⁰ Efficacy, safety, and timing of initiation of contraception after LT have not been well studied, but no obvious contraindication has been reported for estrogen/progestin oral contraceptive use when blood pressure is well controlled (with the exception perhaps of patients with veno-occlusive disease). Intrauterine devices are not recommended in immunosuppressed patients.⁹

Pregnancy after LT is a special clinical consideration that requires further prospective study. LT often results in reversal of chronic liver disease-related secondary amenorrhea and resultant infertility.^{12,13} The effects of immunosuppression on mother, allograft, and fetus during pregnancy are not completely understood.⁹ Although pregnancy outcomes after LT have been reported to be largely favorable, distinct, yet acceptable, risks remain for mother, fetus, and graft. LT centers should continue to report pregnancy outcomes to identify the mechanisms associated with pregnancy-related complications and the LT recipients at high risk for complications. Preoperative and prenatal counseling strategies are limited by a lack of experience and, as a result, have not been standardized.¹⁰ Improved knowledge of these issues is crucial for guiding

informed decision making and may have a significant impact on QOL for female LT recipients.

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